

# Urinary Biomarkers as Exposure Surrogates

## Controlling for Possible Bias

Biomonitoring, or measuring levels of contaminants and their metabolites in human biological samples, can tell researchers a good deal about the environmental agents to which populations are exposed.<sup>1</sup> This information can help identify human health risks associated with environmental exposures, but the accuracy of conclusions hinges on the correct interpretation of the data.<sup>2,3,4</sup> A new study in *EHP* highlights a potential source of bias in estimating exposures on the basis of urine samples and suggests a possible means to control for it.<sup>2</sup>

The study used data collected through the National Health and Nutrition Examination Survey (NHANES), an ongoing program that includes biomonitoring of a nationally representative segment of the U.S. general population.<sup>5</sup> Participants undergo physical examination, provide biological samples such as blood and urine for laboratory testing, and complete interviews regarding health, lifestyle, socioeconomic status, and other variables. NHANES data are then available for analysis by various research groups for the general purpose of evaluating and improving public health.

In NHANES, as well as in biomonitoring studies in general, urine is one of the most commonly used biological specimens.<sup>4</sup> Sample collection is noninvasive, and laboratory analysis can quantify specific environmental contaminants in the sample. However, various factors such as hydration status and physiological differences among individuals can introduce uncertainty when estimating actual exposures from these measurements. For instance, as a result of variables such as these, the same exposure could result in different concentrations of metabolite in two different people's urine. Linking estimated exposures to specific health outcomes represents an additional layer of uncertainty.<sup>2,3</sup>

The authors of the current study used data from the 2009–2010 and 2011–2012 NHANES cycles to assess patterns in the relationship between urinary flow rate (UFR) and body weight–adjusted urinary flow rate (UFRBW). These NHANES cycles differed from previous ones in that they collected data on the time between last and current urination and on urine volume, details that provide a more in-depth understanding of what urinary concentrations of environmental contaminants and their metabolites actually mean. “The issue of adjusting for hydration status in general—how much urine someone is producing over a period of time—is something that people in the biomonitoring community always struggle with in terms of correcting for it,” says coauthor Lesa Aylward, principal at Summit Toxicology LLP.

Given this additional information, the authors explored whether systematic variations exist in UFR (measured in milliliters of urine produced per hour) as a function of age, sex, race/ethnicity, and body mass index (BMI) category. In addition, they tested their hypotheses by focusing on urinary concentrations and analyte excretion rates (measured in nanograms per hour, with and without adjustment for body weight) among different age groups for the chemicals bisphenol A and 2,5-dichlorophenol. They compared the results with those obtained by using conventional estimation methods, such as adjusting measurements based on urine levels of the metabolite creatinine, a surrogate for hydration status.

The NHANES data analyzed in the current study included information on 14,631 participants aged 6 years and older. The authors found that both UFR and UFRBW varied by age and race/ethnicity, whereas only UFR varied by sex, and only UFRBW varied by BMI.<sup>2</sup>



**The findings from a new study may enable researchers to more accurately assess the significance of chemical concentrations in biological samples.**

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This latter relationship illustrates a potential impediment to correctly discerning the relationship between a chemical exposure and a particular health variable: a chemical might affect that variable, but the variable itself might influence the measurement of the chemical. This phenomenon, sometimes called “reverse causation,” is highly relevant to reported associations between environmental chemicals and BMI-related conditions such as obesity, heart disease, and diabetes—many of which have been made based on NHANES data.<sup>6</sup>

As the assessments in the current study demonstrated, calculating analyte excretion rates could offset this problem. It is important to collect the information needed to estimate analyte excretion rates at the time samples are collected; otherwise, adjustments can't be made to the raw data.

The complexity revealed by the findings of the new study is a good thing, says Krista Christensen, an epidemiologist at the Wisconsin Division of Public Health. “This complexity will help researchers to better understand, analyze, and interpret their data—and this article is a great step forward in describing the considerations needed when using urinary biomarker data,” Christensen says. She was not involved in this study but used UFR calculations in another recent study.<sup>3</sup>

Aylward also indicates that the study raises some broader issues. “Biomonitoring data for chemicals has really exploded in the last fifteen years,” she says. “We're now moving into a situation where we have a more sophisticated understanding of the physiological factors that might influence the concentrations of chemicals that can be measured. We're trying to move from being naive consumers of biomonitoring data to being more sophisticated consumers of those data.”

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#### ■ REFERENCES

1. Angerer J, et al. Human biomonitoring: state of the art. *Int J Hyg Environ Health* 210(3–4):201–228 (2007); doi:10.1016/j.ijheh.2007.01.024.
2. Hays SM, et al. Variation in urinary flow rates according to demographic characteristics and body mass index in NHANES: potential confounding of associations between health outcomes and urinary biomarker concentrations. *Environ Health Perspect* 123(4):293–300 (2015); doi:10.1289/ehp.1408944.
3. Christensen K, et al. Changes in epidemiologic associations with different exposure metrics: a case study of phthalate exposure associations with body mass index and waist circumference. *Environ Int* 73:66–76 (2014); doi:10.1016/j.envint.2014.07.010.
4. Esteban M, Castaño A. Non-invasive matrices in human biomonitoring: a review. *Environ Int* 35(2):438–449 (2009); doi:10.1016/j.envint.2008.09.003.
5. NCHS. About the National Health and Nutrition Examination Survey [website]. Hyattsville, MD:National Center for Health Statistics, U.S. Centers for Disease Control and Prevention (updated 3 February 2014). Available: [http://www.cdc.gov/nchs/nhanes/about\\_nhanes.htm](http://www.cdc.gov/nchs/nhanes/about_nhanes.htm) [accessed 16 March 2015].
6. Lakind JS, et al. Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: a systematic review of epidemiologic research. *Crit Rev Toxicol* 44(2):121–150 (2014); doi:10.3109/10408444.2013.860075.